2013 by the American College of Cardiology-American Heart Association (ACC-AHA) Task Force on Practice Guidelines (Stone NJ et al, Circulation 2013 [E-pub ahead of print] doi: 10.1161/01.cir.0000437738.63853.7a). These new guidelines represent a significant departure from previous recommendations that promoted specific lipid-level goals for patients that depended on level of risk. The new guidelines rely heavily on randomized, controlled trials involving fixed doses of statin medications in patients at risk for atherosclerotic cardiovascular disease. Four subgroups of patients were identified where benefits of statins outweigh risk. These included (1) those with clinically evident atherosclerotic cardiovascular disease; (2) primary low-density lipoprotein (LDL) cholesterol levels ≥190 mg/dL; (3) patients with type 1 or type 2 diabetes and LDL cholesterol levels ≥70 mg/dL; and (4) patients with a 10-year risk of atherosclerotic cardiovascular disease of at least 7.5% and an LDL cholesterol level ≥70 mg/dL. In addition, the new guidelines identify patients for whom data do not support statin therapy. These include those aged ≥75 years unless clinical atherosclerotic cardiovascular disease is present, those with a need for hemodialysis, or patients with New York Heart Association class II, III, or IV heart failure. In addition, the panel noted that there was no evidence to support use of nonstatin cholesterol-lowering drugs combined with statin therapy or in statin-intolerant patients.

Comment: Adherence to the new guidelines will result in considerable changes in practice patterns that include avoidance of cholesterol-lowering therapy in certain patient groups and elimination of routine assessments of LDL cholesterol levels in patients receiving statin therapy because target levels are no longer emphasized. Additional changes include avoidance of nonstatin LDL cholesterol-lowering agents, more conservative use of statins in patients aged >75 years, and diminished use of surrogate markers, such as C-reactive protein or calcium scores, for selection of patients for statin therapy. Finally, the use of a new risk calculator in the new guidelines is likely to target larger numbers of patients for statin therapy.

Screening for Peripheral Artery Disease and Cardiovascular Disease Risk Assessment With the Ankle-Brachial Index in Adults: U.S. Preventive Services Task Force Recommendation Statement

Moyer VA, and the U.S. Preventive Services Task Force. Ann Intern Med 2013; 159:342-8.

Conclusions: Current evidence is insufficient to assess the balance of benefits and harms for screening for peripheral arterial disease (PAD) and cardiovascular disease (CVD) risk assessment with ankle-brachial index (ABI) in adults.

Summary: The U.S. Preventive Services Task Force (USPSTF) makes recommendations about effectiveness of specific preventive care services for patients without disease-related symptoms. Recommendations are based on balance of benefits and harm of the potential testing modality with respect to the disease process undergoing evaluation. With respect to PAD, early detection of PAD in asymptomatic patients is primarily considered because subsequent treatment may reduce overall CVD. However, the USPSTF found no evidence that screening for treatment of PAD in asymptomatic patients can provide clinically important benefits. In fact, one randomized trial found that aspirin did not reduce CVD events in patients with low ABI (Fowkes FG et al, JAMA 2010;303:841-8). The same trial found that low-dose aspirin treatment in asymptomatic patients with a low ABI might actually increase bleeding. Additional harms considered by the USPSTF for screening ABI included false-positive results, with the potential of subsequent exposure to gadolinium or a contrast agent if additional studies are used to confirm diagnoses. In addition, patient anxiety and opportunity costs were also considered potential harms. Additional potential harms included the use of unnecessary medications (or higher doses) and the resulting adverse effects of additional medications or increased medication dosages. Most of these potential harms are downstream harms because there is little potential harm associated with conducting the ABI examination itself. This study follows two previous recommendations by the USPSTF against screening for PAD, the first in 1996 and the second in 2005. The current study focused on broader CVD outcomes than previous reviews and specifically focused on resting ABI as the sole screening method. Although the USPSTF found evidence that ABI is a reliable screening test for PAD, the ultimate conclusion was that the evidence to support treatment based on this screening test is inadequate and that there were no studies addressing harms of screening.

Comment: Detection of asymptomatic peripheral arterial disease may identify patients at risk for other types of CVD other than just PAD. However, evidence directly supporting this supposition is lacking. "Therefore the USFPSTF concludes that the evidence on the balance of benefits and harms of screening is lacking." One must also consider that many patients with asymptomatic low ABIs may never develop clinical signs or symptoms of CVD and yet if treated on the basis of the low ABI would be subject to the harms of testing and subsequent treatments. With the exception of screening for abdominal aortic aneurysm, screening for any form of PVD remains controversial.

Carotid Plaque MRI and Stroke Risk: A Systematic Review and Meta-analysis

Gupta A, Baradaran H, Schweitzer AD, et al. Stroke 2013;44:3071-7.

Conclusions: Dedicated magnetic resonance imaging (MRI) of plaque composition offers stroke risk information beyond measurement of luminal stenosis in carotid atherosclerotic disease.

Summary: Stenosis severity is widely used as a marker for stroke risk in patients with atherosclerotic carotid disease. However, evidence also suggests plaque composition can also predict stroke risk independent of stenosis severity (den Hartog AG et al, Eur J Vasc Endovasc Surg 2013;45:7-21). MRI measurements of plaque composition may help characterize carotid plaques with respect to stroke risk. However, individual studies have been relatively small, and it is unclear whether differences in risk profiles of specific plaque components, such as intraplaque hemorrhage, lipid-rich necrotic core, or thinning/rupture of the fibrous cap, contribute differentially to stroke risk. The authors therefore performed a systematic review and meta-analysis to evaluate whether MRI of plaque composition is a predictor of ipsilateral ischemic stroke or transient ischemic attack (TIA) in carotid atherosclerotic disease. A comprehensive literature search evaluated the association of carotid plaque composition on MRI with ischemic outcomes. Included studies were cohort studies examining intraplaque hemorrhage, lipid-rich necrotic core, or thinning/rupture of the fibrous cap with a mean follow-up of ≥1 month and an outcome measure of ipsilateral stroke or TIA. A meta-analysis using a random-effects model assessing study heterogeneity and publication biases was performed. The authors screened 3436 articles, and nine studies with a total of 779 subjects met eligibility for systematic review. Ratios for intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap as predictors of subsequent stroke/TIA were 4.59 (95% confidence interval [CI], 2.91-7.24), 3.00 (95% CI, 1.51-5.95), and 5.93 (95% CI, 2.65-13.20), respectively. There was no significant heterogeneity or publication bias in the three main meta-analyses performed.

Comment: One possible conclusion of this article, given the number of articles potentially available for inclusion in this study and the small number subsequently selected for systematic review, is that there must be remarkable limitations of the current literature on MRI plaque characterization. Therefore, the use of carotid plaque MRI to select high-risk groups potentially benefiting from carotid intervention remains quite problematic at this point. The study does point out that the MRI variables of intraplaque hemorrhage, lipid-rich necrotic core, and thinning of the fibrous cap are targets for future research.

Doxycycline for Stabilization of Abdominal Aortic Aneurysms: A Randomized Trial

Meijer CA, Stigmen T, and the Pharmaceutical Aneurysm Stabilization Trial Study Group. Ann Intern Med. 2013;159:815-23.

Conclusions: Doxycycline therapy for 18 months does not reduce aneurysm growth and does not influence need for aneurysm repair or time to repair.

Summary: Matrix metalloproteinases (MMPs) appear to be involved in abdominal aortic aneurysm (AAA) pathogenesis and pathophysiology. Doxycycline is a nonspecific MMP inhibitor and has been shown to decrease AAA formation and progression in preclinical models of aneurysm disease (Bergqvist D, Eur J Vasc Endovasc Surg 2011;41:663-7; and Dodd BR et al, Curr Vasc Pharmacol 2011;9:4-8). In addition, a small study of 3 months of doxycycline reported reduced aneurysm growth 6 to 12 months later (Mosorin M et al, J Vasc Surg 2001;34:6-10). Finally, a safety trial of 6 months of doxycycline treatment reported that "the observed rate of aneurysm growth compared favorably with that described in natural history studies of aneurysm growth" (Baxter BT et al, J Vasc Surg 2002;36:1-12). Other medical therapies, most prominently β-blockers, have been considered for medical management of disease but have not been conclusively demonstrated to reduce progression of AAAs. Currently, doxycycline is considered to be the lead candidate for potential pharmaceutical stabilization of AAAs. The purpose of this study was to test whether doxycycline inhibits AAA progression in humans. This was a randomized placebo-controlled, double-blind trial conducted in 14 Dutch hospitals. The study recruited 286 patients with small AAAs and randomized 144 to daily doses of 100 mg doxycycline and 142 to placebo for 18 months. The two groups were well balanced with respect to baseline demographic and clinical characteristics. The primary outcome measure was aneurysm growth at 18 months, as estimated by repeated single-observer ultrasound study. Secondary outcome measures included aneurysm growth at 12 months and need

for elective surgery. At 18 months, doxycycline did not decrease aneurysm growth compared with the control group. In fact, there was a small increase in aneurysm growth of 4.1 mm (95% confidence interval [CI], 3.6-4.5 mm) in the doxycycline group vs 3.3 mm (95% CI, 2.8-3.7 mm) in the control group at 18 months. The difference in diameter growth was 0.8 mm (95% CI, 0.1-1.4 mm; $P = .016$). Twenty-one patients receiving doxycycline and 22 receiving placebo had elective surgical repair. Kaplan-Meier estimates for elective surgical repair were 16.1% for those receiving doxycycline and 16.5% receiving placebo; difference, −0.4% (95% CI, −9.3% to 8.5%; $P = .83$). Time to aneurysm repair was also similar in the groups ($P = .92$).

Comment: One of the holy grails of vascular disease is a pill to prevent development of AAAs in patients at risk or slow progression of the AAA in those with small aneurysms. As such, the results of this study are disappointing, because doxycycline has been considered the leading candidate for medical management of aortic aneurysm disease. There is currently in the United States a National Institute of Health-sponsored smaller trial of doxycycline, using twice the dose of doxycycline used in the Dutch trial, for management of small AAAs. The results of this study will not likely be available for several years. Apparently, however, one needs to consider the possibility that our current understanding of the biochemical mechanisms of aneurysm formation may be insufficient to develop a precisely targeted pharmacologic intervention.

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Pirmohamed M, Burnside G, Eriksson N, and EU-PACT Group. N Engl J Med 2013;369:2294-303

Conclusions: Pharmacogenetic-based dosing is associated with a higher percentage of time in therapeutic international normalized ratio (INR) range than standard dosing during initiation of warfarin therapy.

Summary: Warfarin has a wide variation of dosages needed to achieve relatively narrow therapeutic indices. This variation can be due to insufficient or excessive anticoagulation. Polymorphisms in two genes, *CYP2C9* (involved in the metabolism of the pharmacologically more potent S-enantiomer of warfarin) and *VKORC1* (involved in the vitamin K cycle), in combination with age and body surface area, are known to account for ~50% of the variability in the individual daily dose requirements for warfarin (Johnson JA et al, Clin Pharmacol Ther 2011;90:625-9; and Yang J et al, Int J Cardiol 2013;168:4234-43). Indeed, the U.S. Food and Drug Administration changed the drug label for warfarin to include the statement "The patient's *CYP2C9* and *VKORC1* genotype information, when available, can assist in selection of the starting dose for warfarin." (Finkelman BS et al, J Am CollCardiol 2011;57:612-8). However, lack of data from randomized trials has led to the fact that genotyping before a prescription of warfarin is not recommended in clinical practice guidelines (Holbrook A et al, Chest 2012;141(Suppl):e152-84S). There have been prospective studies and randomized trials that failed to show genotyping improves anticoagulation control, but despite these, a recent study also showed that genotype-guided dosing led to superior control of anticoagulation (Anderson JL et al, Circulation 2012;125:1997-2005). In this study, the authors prospectively compared the effect of genotype-guided dosing with that of standard dosing on anticoagulation control in patients starting warfarin therapy. This was a multicenter, randomized, control trial involving patients with atrial fibrillation or venous thromboembolism. Genotyping for *CYP2C9*2*, *CYP2C9*3*, and *VKORC1* (−1639G→A) was performed using a point-of-care test. For patients assigned to the genotype-guided group, warfarin doses were prescribed according to pharmacogenetic-based algorithms for the first 5 days. Patients in the standard-dosing group (controls) received a 3-day loading-dose regimen. After the initiation period, treatment management of all patients was according to routine clinical practice. The primary outcome measure was the percentage of time in the therapeutic range, with 2.0 to 3.0 the goal for the INR during the first 12 weeks after initiation of warfarin therapy. The study recruited 455 patients, and 227 were randomly assigned to the genotype-guided group and 228 to the control group. The mean percentage of time in the therapeutic range was 67.4% in the genotype-guided group compared with 60.3% in the control group (adjusted difference, 7.0 percentage points; 95% confidence interval, 3.3-10.6; $P < .001$). Significantly fewer incidences of excessive anticoagulation (INR ≥4.0) occurred in the genotype-guided group. Median time to reach therapeutic INR was 21 days in the genotype-guided group compared with 29 days in the control group ($P < .001$).

Comment: The trial has a number of weaknesses, including the fact that the majority of patients are of European ethnic background and the results can therefore perhaps not be generalized to other ethnic groups. But most importantly, the outcome measure was time in so-called therapeutic range rather than clinical outcome measures of bleeding and thrombosis. Whether genotype-guided dosing of warfarin therapy can lead to improved clinical outcomes in a setting outside of a clinical trial remains to be determined. Indeed, the future role of warfarin anticoagulation in the era where not all anticoagulation agents will not require monitoring will remain to be determined. It may be, in the future, that many of the patients included in this trial will not even be considered for warfarin anticoagulation but will be preferentially treated by the new oral activated 10a inhibitors.

A Risk Prediction Model for Determining Appropriateness of CEA in Patients With Asymptomatic Carotid Artery Stenosis

Conrad MF, Kang J, Mukhopadhyay S, et al. Ann Surg 2013;258:534-40.

Conclusions: A scoring system based on the probability of long-term survival can be used to determine patients most likely to benefit from carotid endarterectomy (CEA).

Summary: There is considerable controversy about which patients with asymptomatic carotid stenosis, even high-grade asymptomatic carotid stenosis, are most likely to benefit from a prophylactic CEA. Indeed, there are those who believe that asymptomatic carotid stenosis may be best treated with carotid artery stenting and those who also contend that with modern medical therapy, asymptomatic carotid stenosis may be best treated with medical therapy alone. Although it seems intuitive that life expectancy should be considered in the decision to perform prophylactic CEA, there are also a number of other variables, such as plaque morphology, degree of ipsilateral carotid stenosis, degree of contralateral carotid stenosis, presence and number of asymptomatic cerebral infarcts, and patient willingness and ability to adhere to maximum medical management of atherosclerotic risk factors, that all can play a role in the decision to perform prophylactic CEA. Indeed, the authors point out that a recent document from the Society for Vascular Surgery reported to guide clinical research goals for the next 10 years indicated that optimal management of asymptomatic carotid stenosis was the top priority (Kraiss LW et al, J Vasc Surg 2013;57:493-500). The goal of this study was for the authors to create a scoring system to predict 5-year survival after CEA that would be useful in selecting, or at least helping to select, patients with asymptomatic carotid stenosis for prophylactic CEA. The data were based on patients who underwent CEA for severe asymptomatic carotid stenosis from 1989 to 2005 at the authors' institution. Long-term survival of these patients was determined by a review of hospital records and the Social Security Death Index. All patients had a potential for at least 5 years of follow-up. A logistic regression of predictors of survival at 5 years was performed, and the odds ratios associated with the analysis of significant comorbidities were used to create a scoring system to predict survival. The scoring system was then validated within the cohort using the Hosmer-Lemeshow test and a derivation/validation receiver operating characteristic (ROC) curve. There were 2004 CEA procedures performed in 1791 patients. The average follow-up was 130 ± 49 months. Eighty-four percent of the patients were hypertensive, 56% had coronary artery disease, 24% diabetes, and 71% were taking statins. The 30-day stroke rate was 1.1%, and the mortality rate was 0.7%. Actual 5-year survival was 73%. Predictors of death by logistic regression analysis were age by decade (odds ratio [OR], 1.8; $P < .0001$), coronary artery disease (OR, 1.5; $P = .0007$), chronic obstructive pulmonary disease (OR, 2.5; $P < .0001$), diabetes (OR, 1.7; $P < .0001$), neck radiation (OR, 2.6; $P = .005$), no statin (OR, 2.1; $P < .0001$), and creatinine >1.5 mg/dL (OR, 2.6; $P < .0001$). The variables were then assigned a hierarchal point scoring system in accordance with the OR value. The 5-year survival based on the scoring system was 0 to 5 points, 92.5%, 6 to 8 points, 83.6%; 9 to 11 points, 63.7%; 12 to 14 points, 46.5%; and >15 points, 33.8%. The Hosmer-Lemeshow test validated the scoring system ($P = .26$), and there was no difference in the ROC curves (C statistic, 0.74 vs 0.73).

Comment: Like many surgical series, the data here are highly prejudiced in that they were derived from patients who actually had a CEA and were from only a single institution in the Northeast. The potential for unrecognized confounding variables possibly influencing the logistic regression analysis is therefore high. The authors' data suggest they may be fairly conservative in selecting their patients, because the highest risk score for 5-year survival among their patients was 18, with a maximum possible score of 35. Perhaps the most salient feature of this report is to demonstrate to our medical colleagues that surgeons really do try to exercise judgment in their selection of patients for CEA. Selection of patients for CEA with reasonable life spans is certainly part of that judgment, but perhaps selection of patients at most risk for disabling stroke or stroke-related death is also part of that judgment.